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ABSTRACT

This document consists of the first six issues of a newsletter, which discusses current knowledge about and concerns related to genetics and mental retardation. The second issue addresses the problem of genetic discrimination. The third issue considers genetic testing, screening, and counseling. The fourth issue addresses genetic privacy issues. The fifth issue discusses Fragile X syndrome. The sixth issue discusses genetherapy and mental retardation. (DB)

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# Genetic Issues In Mental Retardation

ED 425 562

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*A Report on The Arc's Human Genome Education Project*

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The Arc

# Genetic Issues In Mental Retardation

*A Report on The Arc's Human Genome Education Project* Vol. 1, No. 1

*The Arc's Human Genome Education Project is part of the U.S. Human Genome Project, which is an international effort to identify all the genes within the human body. The goal of The Arc's project is to promote education and discussion of the ethical, legal and social concerns resulting from innovative genetic research. It is funded through the U.S. Department of Energy's ELSI (Ethical, Legal and Social Implications) program.*

## An Introduction to Genetics and Mental Retardation

### The Human Genome Project

The Human Genome Project (HGP) is an international effort involving hundreds of scientists who are attempting to map all 60,000 -- 100,000 human genes. Doing so would be the first step to unlock the nature of human life, shining light on its secrets and mysteries. The project, which is being directed by the National Institutes of Health (NIH) and the Department of Energy (DOE), began in 1990. Its ambitious goal is to identify all genes within the human body by the year 2005. Aside from gene identification, the project is also attempting to identify and answer specific ethical questions related to the consequences of new genetic findings within society. The hope is to begin developing policy options which can address the ethical questions sparked by the project.

### The Arc's Human Genome Education Project

Imagine being able to pinpoint the source of every genetic disorder affecting mankind. For The Arc, the secrets of genetic disorders related to mental retardation could be uncovered. The Human Genome Project could provide a possible future of treatments and cures of some forms of mental retardation.

The Arc received funding from DOE to educate its members and leaders about the ethical, legal and social implications of genetic knowledge and use. As a result, issues can then be evaluated and discussed, and positions developed, based on adequate understanding.

The Arc's involvement stems from the fact that many mental retardation disorders have a genetic cause. As genes causing mental retardation are discovered, the possibility of treatments, cures and genetic testing for inherited conditions raise ethical dilemmas regarding such areas as privacy, fairness and discrimination.

To address these issues, three percent of DOE's overall Human Genome budget is devoted specifically to funding research focusing on the impact of Ethical, Legal and Social Implications (ELSI) of new genetic findings within society. The ELSI program seeks to involve concerned individuals and groups -- like The Arc -- who are directly affected by genetic research. Specific ELSI issues addressed by The Arc's project include:

- Discrimination in insurance and employment
- Genetic testing, screening and counseling
- Genetic therapies to "cure" mental retardation

The Arc's mission is to carry out the following objectives:

- Develop and disseminate educational material for members and leaders of The Arc to inform them about the HGP and mental retardation.
- Conduct training for The Arc's leaders on the scientific, ethical, legal and social aspects of the HGP and mental retardation who can, in turn, provide training to their state and local chapter's membership.
- Disseminate educational material to other disability organizations and the general public as appropriate.

## Ethical, Legal and Social Concerns Arising from New Genetic Findings

Why should The Arc become involved in ethical discussions about genetics? Many mental retardation disorders have genetic causes, with Down syndrome and fragile X syndrome being the most common. (See "Genetic Causes of Mental Retardation" for other mental retardation disorders with genetic causes.) More than 350 inborn errors of metabolism have been identified, most of which lead to mental retardation. Specific genes have already been discovered for a number of single gene conditions, including fragile X syndrome, for which a treatment may be a possibility in the future.

There is a long history of discrimination against people with mental retardation, ranging from the eugenics movement resulting in involuntary sterilization, to the practice of allowing infants born with Down syndrome to die from lack of medical treatment, to the current call to harvest organs of babies born with anencephaly for transplant purposes, even though the infant has not been declared dead.

With this history of discrimination, it is imperative that the scientific and medical community hear the views of consumers and families regarding ethical issues involving new genetic findings. We will prepare educational materials and offer training and opportunities for our association to consider such questions as:

- Must a physician offer prenatal genetics screening to all pregnant women (or risk medical malpractice liability if he or she doesn't)? Does a woman have a right to refuse prenatal screening?
- Should genetic testing be offered when there is no treatment? What about access to testing for poor people?
- What rights does a child have to agree to or refuse testing? Who has rights to the test results? Are parents endangering their child's future employability and insurability? What about psychological harm to the child? (Your young teenage daughter learns she's a carrier for fragile X syndrome, for example.)

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• How can the confidentiality of test results be maintained to prevent insurers from discrimination? Can employers discriminate on the basis of a person's genes?

• Should therapies for genetic conditions causing mental retardation even be considered? Is there positive value in diversity? How can we avoid stigmatizing those living with a genetic condition while trying to eliminate the condition in others? Are some conditions so destructive to the individual that if a therapy is possible it should be undertaken?

• Should you include your newborn child in experimental gene therapy research? Do any guidelines exist to help you make this difficult decision?

These are some examples of the challenging issues The Arc will be addressing throughout the two-year project. With the scientific community often basing their decisions on their beliefs about quality of life of a person with mental retardation, The Arc must participate in the discussions on the ethical, legal and social issues regarding use of genetic knowledge.

**Genetic Disorders Associated with Mental Retardation** with an Estimated Incidence in Excess of 1:100,000

| Diagnosis | Type of disorder | Genetics | Incid./1,000 |
|---|---|---|---|
| Down syndrome | Chromosomal | | 1.30 |
| Fragile X | Single gene | Triplet repeat* | 0.60 |
| Duchenne muscular dystrophy | Single gene | X-linked recessive | 0.15 |
| Trisomy 13 | Chromosomal | | 0.125 |
| Tuberous sclerosis | Single gene | Autosomal dominant | 0.1 |
| Phenylketonuria (PKU) | Single gene | Autosomal recessive | 0.067 |
| Cri du chat | Chromosomal | | 0.05 |
| Galactosemia | Single gene | Autosomal recessive | 0.017 |
| Hunter syndrome | Single gene | X-linked recessive | 0.01 |

*Triplet repeat diseases are inherited in a unique way. The genetic defect can worsen as the gene is passed from one generation to the next. Triplet repeat is named by the three-letter sequences of DNA code which are repeated too many times in the genes causing disorders.

SOURCE: Moser, H.W. (1995) "A Role for Gene Therapy in Mental Retardation," *Mental Retardation and Developmental Disability Research Reviews*. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

## Genetics: An Introduction

Children resemble their parents and relatives, and these traits are passed on for generations. In other words, a child may have his father's nose, her mother's eyes, and those traits might be passed along to that child's child and so on for generations. Biologically this is called inheritance, and genetics is the biology of inheritance. Geneticists study the mechanisms of hereditary transmission -- and sometimes the variations -- of human characteristics.

The characteristics we inherit and pass on are contained within the nucleus of our cells, and the human body is composed of 100 trillion cells. The cell's nucleus carries a blueprint for life composed of contributions of the ancestors who preceded us. That blueprint is in our chromosomes -- our genetic code. The genes on our chromosomes determine our physical and biochemical properties; in effect, our genetic inheritance.

The tens of thousands of genes carried on our chromosomes determine everything from what an individual cell's job is -- whether the cell is a skin cell, a heart muscle cell or a brain cell -- to our physical and developmental characteristics. This complete set of 46 chromosomes is called the cell's genome.

## Genetic Causes of Mental Retardation

With up to 100,000 genes encoded in each cell and 100 trillion cells making up the human body, people are a mind boggingly complex organism. Add to that the constant division and replication of those cells as part of their natural life spans and it is amazing that more things don't go wrong.

Because of this complexity, there are no easy answers to the question of what causes mental retardation. It is attributable to any condition that impairs development of the brain before birth, during birth or in the childhood years. It is caused not only by the genotype or genetic make-up of the individual, but also by the possible influences of environmental factors. Those factors can range from drug use or nutritional deficiencies to poverty and cultural deprivation. As many as 50 percent of people with mental retardation have been found to possess more than one causal factor.

In 30 percent of people with severe mental retardation, the cause of mental retardation remains unknown. When compared to those severely affected, identifying the cause of mental retardation in children mildly affected is much more difficult. Roughly 90 percent of all cases of mental retardation fall within the mild range. Some research has determined that in 75 percent of children with mild mental retardation the cause is unknown.

Most identifiable causes of severe mental retardation originate from genetic disorders. Since the brain is such a complex organ, there are many genes involved in its development. Therefore, there are many different genetic causes of mental retardation. Up to 60 percent of severe mental retardation can be attributed to genetic causes making it the most common cause. (See table for an overview of the more common genetic disorders associated with mental retardation.)

Genetic disorders are generally associated with mental retardation, chronic health problems and developmental delay. In order to have a better understanding as to how genetic disorders occur, they are typically broken down into three types: Chromosomal, single-gene and multifactorial. Two of the most common genetically transmitted forms of mental retardation include Down syndrome (chromosomal disorder) and fragile X syndrome (single-gene disorder).

*Chromosomal disorders* affect approximately 7 out of every 1,000

infants. The disorder is caused by a person having too many or too few chromosomes, or when there is a change in the structure of a chromosome. Half of all first-trimester miscarriages or spontaneous abortions occur as a result of a chromosome abnormality. If the child is born, he or she usually has multiple birth defects and mental retardation.

Most chromosomal disorders happen sporadically. They are not necessarily inherited (even though they are considered genetic disorders). Only a few specific types are inherited in the same way single-gene disorders are inherited. In order for a genetic condition to be inherited, the disease-causing gene must be present within one of the parent's genetic code. In chromosomal disorders, each of the parent's genes is normal. However, during cell division an error in separation, recombination or distribution of chromosomes occurs. Examples of chromosomal disorders include Down syndrome, Trisomy 13, Trisomy 18 and Cri du chat.

*Single-gene disorders* (sometimes called inborn errors of metabolism or Mendelian disorders) are caused by non-working genes. These disorders of metabolism occur when cells are unable to produce proteins or enzymes needed to change certain chemicals into others, or to carry substances from one place to another. The cell's inability to carry out these vital internal functions often results in mental retardation.

Although many conditions are generally referred to as "genetic disorders," single-gene disorders are the most easy to identify as true genetic disorders since they are caused by a mutation or change within a single gene. Single-gene disorders are considered to be potentially the most responsive to gene therapy since they are caused by a mutation within a single gene, as opposed to being caused by mutations within several different genes.

Approximately 1 in 1,500 children are born with defective enzymes resulting in inborn errors of metabolism. Over 7,000 genetic disorders have been identified and catalogued, with up to five new disorders being discovered every year. Though rare, there is a one in 500 chance for a child inheriting this type of disorder.

Single-gene disorders are inherited in one of three ways:

1) Dominant Inheritance. This occurs when a person has a dominant, disease-causing gene which causes abnormalities even if coupled with a "normal" gene. An example associated with mental retardation is tuberous sclerosis.

2) Recessive Inheritance. This occurs when there are two copies of a non-working gene. Parents of children with autosomal recessive conditions are called "carriers" since each parent carries one copy of a disease gene. They show no symptoms of having a disease gene and remain unaware of this until having an affected child. Single-gene disorders are usually classified as autosomal recessive disorders and can be discovered prenatally if the mother is at risk for this genetic condition. Examples associated with mental retardation include phenylketonuria (PKU) and galactosemia.

3) X-linked disorders. These affect those genes located on the X chromosome and can be either X-linked recessive or X-linked dominant. Because there are so few X-linked dominant disorders, more attention is generally paid to X-linked recessive disorders.

The X-linked recessive disorder is also referred to as a sex-linked disorder since it involves genes located on the X, or female, sex chromosome. Since females have two X chromosomes, they are usually unaffected carriers and are less likely than males to show any symptoms of the disorder. On the other hand, males have only one X chromosome and, therefore, cannot be carriers of X-linked recessive disorders. If a male inherits an X-linked recessive disorder, he is affected. Some examples associated with mental retardation include fragile X syndrome, Hunter syndrome, Lesch Nyhan syndrome and Duchenne muscular dystrophy.

Combinations of multiple gene and environmental factors leading to mental retardation are called *multifactorial disorders*. They do not follow a normal inheritance pattern and no one knows exactly why they occur. They are inherited (passed on throughout family generations) but do not share the same characteristic inheritance patterns of single-gene disorders.

Their inheritance patterns are usually much more complex than those of single-gene disorders because their existence depends on the simultaneous presence of several heredity and environmental factors. For example, weight and intelligence are inherited in this way. These disorders are very common and cause a majority of birth defects. Examples of multifactorial disorders include heart disease, diabetes, some cancers, spina bifida, anencephaly, cleft lip and cleft palate, clubfoot and congenital heart defects.

*Becoming familiar with the genetic causes of mental retardation paves the way for more thorough discussions of ethical issues involving genetic research. For example, how will the discovery of new genes associated with mental retardation impact those individuals who have mental retardation? How will individuals who carry a gene for mental retardation, but who show no symptoms of a disorder, be affected?*

*Knowing how mental retardation is genetically inherited opens the door for a clearer understanding and more educated discussions about the ethical issues involved with genetic research. Upcoming reports will address these issues in greater depth by highlighting some of the more common genetic disorders associated with mental retardation.*

*By focusing on these specific disorders, those ethical questions most applicable to The Arc's membership can be defined and discussed. Ultimately, these discussions prepare The Arc to confidently tackle genetic and ethical issues by developing carefully thought out positions related to the use of innovative genetic research.*

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The following resources can be helpful for those seeking additional information on the Human Genome Project and other topics related to genetic research.

**Alliance of Genetic Support Groups**
35 Wisconsin Circle, Suite 440
Chevy Chase, MD 20815
301-652-5553
1-800-336-4363 (1-800-336-GENE)
Contact: Mary Davidson, Executive Director

Provides information for individuals affected by genetic conditions and their families, as well as the public or media and professionals. They provide peer support, professional counseling, crisis intervention, referrals for non-medical services and genetic counseling. Technical assistance is offered to those interested in forming a group or chapter and in fundraising. They maintain a database of support groups on specific genetic disorders and publish a *Directory of National Genetic Voluntary Organizations*.

**National Organization for Rare Disorders (NORD)**
P.O. Box 8923
New Fairfield, CT 06812
203-746-6518
1-800-999-6673 or 1-800-999-NORD
Contact: Abbey S. Meyers, President
http://www.w2.com

Provides information about symptoms, causes, treatments for those affected by a genetic disorder and research on more than 5,000 rare disorders. Also provides assistance in forming support groups or chapter bylaws and fundraising, and referrals to appropriate organizations. Maintains a registry of affected individuals and research grants (linking researchers with families).

**Council of Regional Networks for Genetic Services (CORN)**
Emory University
Pediatrics/Medical Genetics
2040 Ridgewood Drive
Atlanta, GA 30322
404-727-1475
Contact: Cynthia Hinton, M.S., M.P.H., CORN's Project Coordinator

CORN is a consortium of genetic service providers whose goal is to improve access to genetic services and enhance the quality of these services. There are ten regional networks nationwide which provide opportunities for consumers and professionals to communicate and become active in shaping genetic services in their region and nationally.

**National Center for Human Genome Research**
Building 31, Room B1C35
9000 Rockville Pike
Bethesda, MD 20892
301-402-4570
Contact: Leslie Fink
http://www.nchgr.nih.gov

Provides timely information about the progress of the Human Genome Project, as well as numerous written materials and other resources.

**Human Genome Management Information System (HGMIS)**
Oak Ridge National Laboratory
1060 Commerce Park, MS 6480
Oak Ridge, TN 37830
423-576-6669
http://www.ornl.gov/hgmis/

Facilitates genetic research and education for the U.S. Department of Energy (DOE) Human Genome Program Task Force. Staff answer questions about the genome project and provide general information through an information clearinghouse. Produces numerous publications on the project, including a newsletter and the Primer on Molecular Genetics.

**Primer on Molecular Genetics**
by Denise Casey
1991-1992 DOE Human Genome Report
Contact: HGMIS (above)
http://www.gdb.org/Dan/DOE.intro.html

A good overview of genetics, including the basics of DNA, genes and chromosomes, is clearly explained in this document, especially as this information relates to genetic research being conducted by the Human Genome Project. It is a popular resource for teachers, genetic counselors and educational organizations.

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Additional Genetic Information Available on the Internet

**DOE Office of Health and Environmental Research (OHER) Home Page for the DOE Human Genome Program**
http://www.er.doe.gov/production/oher/oher-top.html

Provides information on DOE's Human Genome Project and other OHER projects and links to other program-related sites.

**National Center for Genome Resources (NCGR)**
http://www.ncgr.org

NCGR's Genetics and Public Issues program covers a wide array of genetic information.

*For more information, contact:*

The Arc of the United States
**500 E. Border St., S-300**
**Arlington, Texas 76010**
**(817) 261-6003**
**TDD (817) 277-0553**
**Http://TheArc.org/welcome.html.**

*Produced by The Arc's Human Genome Education Project, Sharon Davis, Ph.D., Principal Investigator and Leigh Ann Reynolds, Project Associate. Funded by the U. S. Department of Energy ELSI Program under Grant No. DE-FG03-96ER62162. Support from DOE does not constitute an endorsement of the views expressed in this publication. October 1996 - Rev. Dec. 1996*

The Arc®

# Genetic Issues In Mental Retardation

*A Report on The Arc's Human Genome Education Project* Vol. 1, No. 2

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## Genetic Discrimination

### Why Should We Care?

Discrimination based on the presence of a disability has always been an issue of great concern to The Arc. People with mental retardation have, for example, long been discriminated against in both insurance and employment. Now a different type of discrimination is emerging due to the increasing use of genetic testing for the purpose of exposing the presence of any abnormal or defective genes. This new phenomenon is called genetic discrimination.

Discrimination based on genetic characteristics includes those individuals who have a gene or genes predisposing them or their offspring to developing diseases, conditions or late-onset disorders. Late-onset refers to disorders which may not show visible signs until later in the individual's life. One example is Huntington disease, a progressive genetic disorder characterized by late-onset neurological symptoms typically arising in the third to fourth decade of life.

Genetic discrimination occurs when someone is treated differently, not based on having a disability, but based on having a gene that may (or may not) cause the person to show symptoms of a disability sometime in the future. In other words, genetic discrimination occurs when people are treated differently because they have the gene or genes, even when they show no symptoms of disease. Men and women who are carriers for a genetic condition (who show no signs of disease) may also be discriminated against because of their potential to have a child with a genetic condition.

With the passage of the Americans with Disabilities Act (ADA) in 1990, discrimination based on the presence of a disability is now against the law. The ADA may protect against genetic discrimination as well since the law applies not only to people with a disability, but also to people *regarded* as having a disability. People who experience genetic discrimination are often regarded as having a disability (because they have an abnormal gene), even though they may not. The Equal Employment Opportunities Commission (EEOC) ruled in 1995 that genetic discrimination in employment is prohibited. However, the ADA does not prohibit insurance companies from denying coverage to people who carry defective genes if, based on state law, they have evidence to determine the risk of covering an individual.

The Arc's Human Genome Education Project is promoting education and discussion of the ethical, legal and social concerns resulting from new discoveries about the human genome. One aspect of the project focuses on genetic discrimination, especially as it relates to the ability to obtain and keep health insurance and employment. Because people with mental retardation experience discrimination based on having a disability rather than discrimination based on having disease-causing genes, these issues do not directly impact them. However, family members of a person with mental retardation, or carriers of a genetic condition associated with mental retardation, need to be aware of the possibility of being discriminated against based on their genetic make-up.

This volume of *Genetic Issues in Mental Retardation* covers information related to genetic discrimination, including an explanation of its effects and information that may help protect you and your family from being the target of discrimination.

### Key Points Related to Genetic Discrimination

- Genetic discrimination means that individuals are treated differently based on actual or perceived genetic differences, as distinguished from being discriminated against based on actually having a disease or condition that is genetically caused.
- A recent study noted more than 200 instances of genetic discrimination in areas such as health insurance, employment and adoption.
- The scientific community's ability to test for disease-causing genes is advancing rapidly, much faster than our ability to treat the disease condition.
- We all have several defective genes that place us at risk of genetic discrimination. Some members of The Arc learned of their gene-carrying status when they had a child who inherited a gene that caused mental retardation.
- Just because we have a gene or genes predisposing us to a genetic disease does not mean we will get the disease. A variety of environmental factors (such as geographic location, general nutritional state, personal health habits, socioeconomic level, access to health care and exposure to pollutants and chemicals) also play a major role.
- States and the federal government have begun to enact laws prohibiting genetic discrimination. The Americans with Disabilities Act (ADA) may offer protection to people regarded as having a disability because they have a defective gene. Guidelines for policymakers to ban genetic discrimination have been proposed.

# Facts About Genetic Discrimination

## What is genetic discrimination?

Genetic discrimination describes the differential treatment of individuals or their relatives based on their actual or presumed genetic differences as distinguished from discrimination based on having symptoms of a genetic-based disease (Geller, et al, 1996). Genetic discrimination is aimed at people who appear healthy or whose symptoms are so mild that their functioning and health are not affected. Such individuals may include people who carry the gene for fragile X, the most common inherited cause of mental retardation. Twenty percent of people with this gene will never display any form of mental retardation. Yet, because they carry the gene for fragile X, they could be treated as though they had mental retardation even though they do not (Boyle, 1995).

## Why is concern about genetic discrimination increasing?

The Human Genome Project, a collaboration of scientists worldwide, is conducting research to find the location of the 100,000 or so human genes by the year 2005. Understanding the complete set of genes, known as the human genome, will lead to precise new approaches to the diagnosis, treatment and prevention of disease. Errors in our genes are responsible for an estimated 3000 to 4000 clearly hereditary diseases and conditions. They play a part in cancer, heart disease, diabetes and many other common conditions, such as mental retardation. Within the next five to ten years we may be able to discover almost all of the diseases we are at risk of inheriting.

Genetic testing can be harmful if the information is used to deny jobs or insurance or if it leads to other forms of discrimination. According to Francis S. Collins, Director, National Center for Human Genome Research (1995), "all of us carry probably four or five really fouled-up genes and another couple of dozen that are not so great and place us at risk for something (p. 16)." However, although everyone has a few defective genes, not everyone will be affected. Multiple factors within the environment have a significant impact on a person's health. These factors, either alone or combined with a disease-causing gene, can increase or decrease an individual's risk of developing a disease (Nelson-Anderson & Waters, 1995).

## Legislation on Genetic Discrimination Within the United States*

| State | Enacted Bills | Pending Bills | Defeated Bills |
|---|---|---|---|
| Alaska | | | Health Insurance |
| California | Health Insurance | Employment | |
| Colorado | Health Insurance & Group Disability | | |
| Connecticut | | | Health Insurance & Employment |
| Florida | | | Health and Life Insurance |
| Georgia | Health Insurance | | |
| Hawaii | | Health, Life Insurance & Employment | |
| Iowa | Employment | | |
| Illinois | | Employment | Health Insurance |
| Indiana | | | Health Insurance |
| Kansas | | | Health Insurance & Employment |
| Maryland | Health Insurance | | |
| Massachusetts | | Health, Life & Disability Insurance | |
| Michigan | | All Insurance & Employment | |
| Minnesota | Health Insurance | | |
| Nebraska | | | Health Insurance |
| New Hampshire | Employment | | |
| New Jersey | Health Insurance & Employment | | |
| New York | Employment | Health Insurance | |
| Ohio | Health Insurance | | |
| Oklahoma | | | Health Insurance & Employment |
| Oregon | Health Insurance & Employment | | |
| Pennsylvania | | Health Insurance | |
| Rhode Island | Employment | | |
| Texas | | | Health Insurance & Employment |
| Virginia | Health Insurance | | |
| Wisconsin | Health Insurance & Employment | | |

** This information was taken from "Genetic Discrimination Legislation: Enacted, Pending, and Defeated State Legislation (July 1996)." Contact the Council for Responsible Genetics (CRG) for detailed, up-to-date information within your state.*

## Where is genetic discrimination happening?

A recent study which questioned people with defective genes that could lead to a disease, but who had no symptoms, found that genetic discrimination occurred in many settings (Geller, et al, 1996). As a result, people who fear potential genetic discrimination may be discouraged from obtaining genetic

information that could bring health benefits to them and their families.

One of the most common forms of discrimination is denial of health insurance based on a person's genes. Insurance companies gather and use medical information to predict a person's risk of illness and death. They use this "risk" information to determine which individuals and groups they will insure and at what price. That information plays a critical role for people in determining access to health care.

Employment is another area with reported cases of discrimination. Many individuals believe they were not hired or were fired because they were at-risk for genetic conditions. In other cases, individuals who were employed were reluctant to change jobs because they feared losing health insurance coverage (Geller, et al, 1996). Having a defective gene could be considered a pre-existing condition by insurance companies who, on that basis, may deny coverage. Recently passed federal legislation places limitations on the exclusion period for pre-existing conditions when people change jobs (The Health Insurance Portability and Accountability Act of 1996).

Discrimination has also occurred when medical professionals counseled individuals about child bearing by urging prenatal diagnostic testing or telling them they should not have children. Similarly, some adoption agencies have unfairly treated prospective parents with a genetic condition by refusing adoption or assuming they should adopt only children at risk of inheriting a disability (Geller, et al, 1996).

## Doesn't the ADA protect people against genetic discrimination?

The Americans with Disabilities Act (ADA) offers protection from discrimination to individuals *currently affected* by a genetic condition or disease. It also applies to individuals who are *regarded* as having a disability. The Equal Employment Opportunities Commission, which oversees enforcement of nondiscrimination in employment, has ruled that ADA applies specifically to individuals who are subjected to discrimination on the basis of genetic information relating to illness, disease, condition or other disorders (EEOC, 1995). This interpretation extends coverage to people who have genes making them predisposed to a disease-causing disability or who have genes for a late-onset disorder. However, it may not protect carriers of genetic disorders who do not yet manifest symptoms of a disease (the "unaffected carrier"). They may be discriminated against based on concerns about health costs of future affected dependents.

The Americans with Disabilities Act does not cover the insurance industry. Insurance companies may deny health, life, disability and other forms of insurance to people with defective genes if there is a sound basis for determining risks consistent with state law. Health maintenance organizations can also refuse to cover an individual with a genetic diagnosis even if the individual has no symptoms of the genetic disorder, provided there is a sound basis for the decision based on actual risk experience (Alper and Natowicz, 1993).

## What are the implications of genetic information for family members?

When people learn that they have a gene that places them at increased risk for certain diseases, they face the dilemma of whether or not to tell other family members about their potential susceptibility to disease. This information is directly relevant to their biological relatives, for other family members may also have the gene and be at increased risk. It also has implications for family members being at risk of genetic discrimination, since genetic information about an individual is also information about that person's family.

Genetic information may profoundly affect people's decisions about having children. There is also evidence that some individuals who have defective genes are stigmatized, suffering a loss of social and economic opportunities (NIH-DOE Working Group on Ethical, Legal, and Social Implications of Human Genome Research, 1993).

## What steps are being taken to eliminate genetic discrimination?

In addition to federal law and regulations, several states have developed and adopted legislation banning discrimination in health insurance and employment. Currently eleven states have laws prohibiting health insurers from denying health care coverage because of a genetic condition. Seven states prohibit employers from requiring genetic tests or using genetic health predictions in employment decisions. Seven other states have bills pending to protect individuals from discriminatory use of genetic information in employment practices or for insurance purposes (Council for Responsible Genetics, 1996). Refer to the table "Legislation on Genetic Discrimination within the United States" for a brief overview of state legislation.

As noted earlier, the Federal Health Insurance Portability and Accountability Act of 1996 offers protections against discrimination in health insurance by limiting pre-existing condition exclusions. It also prohibits discrimination against individuals based on health status, including their genetic information.

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The Health Insurance Portability and Accountability Act of 1996, Pub.L. No. 104-191, Title 1, Sec. 101 and 102, 104th Cong. (1996).

## Guidelines for Developing Policies to Ban Genetic Discrimination

The following guidelines were developed by the NIH-DOE Working Group on the Ethical, Legal, and Social Implications of the Human Genome Project and the National Action Plan on Breast Cancer to assist policy makers in developing legislation to protect individuals from genetic discrimination in insurance. They have been endorsed by the National Advisory Council on Human Genome Research.

1. Insurance providers should be prohibited from using genetic information, or an individual's request for genetic services, to deny or limit any coverage or to establish eligibility, continuation, enrollment, or contribution requirements.

2. Insurance providers should be prohibited from establishing differential rates or premium payments based on genetic information or an individual's request for genetic services.

3. Insurance providers should be prohibited from requesting or requiring collection or disclosure of genetic information.

4. Insurance providers and other holders of genetic information should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure would be made.

## Case Examples of Genetic Discrimination

### *What Would You Do?*

• A mother suspects her young son may have a learning disability. She consults her doctor. Her doctor performs some genetic tests and discovers that the child has fragile X syndrome, the most common genetic cause of mental retardation. Her insurance company eliminates the boy's coverage, claiming that his disability represents a pre-existing condition (Council for Responsible Genetics, Position Paper on Genetic Discrimination).

*You suspect your other child may have the same disability. Would you decide to have your other child tested for this condition even though the child could lose his or her health care coverage?*

• A private insurer in Colorado notified parents of a three-year-old child, who had been recently diagnosed with a syndrome associated with mental retardation, that the child's policy was terminated even though the family had been on the policy for nine months before the diagnosis.*

*What legal rights do you have in your state that can protect your child from this type of genetic discrimination? Can the ADA protect you from genetic discrimination?*

• An HMO had covered the medical expenses of a child since birth but refused to pay for occupational therapy after she was diagnosed with a condition associated with mental retardation, claiming the condition was pre-existing. All bills relevant to the condition had been paid up to the time of diagnosis.*

*If the child has not shown any outward signs of having the condition, is it fair for the insurance company to deny the child medical benefits based on his or her genes alone?*

***Geller, L., Alper, J., Billings, P., Barash, C., Beckwith, J. & Natowicz, M. (1996). Individual, family and societal dimensions of genetic discrimination: A case study analysis. Science and Engineering Ethics, 2, 71-88.**

## Helpful Resources

**Council for Responsible Genetics (CRG)**
**5 Upland Road, Suite 3, Cambridge, Mass. 02140**
**(617) 868-0870 http://www.essential.org/crg**

The CRG is a national non-profit organization representing over 1,000 scientists, bioethicists and religious leaders who are concerned about the social and ethical implications of new genetic technologies. They document cases of genetic discrimination and civil liberties abuses that occur as a result of genetic testing and DNA profiling.

**The Genome Action Coalition**
**317 Massachusetts Avenue, N.E., Suite 100**
**Washington, D.C. 20002 (202) 546-4732**
**Contact: Lyle Dennis**

The purpose of this voluntary association of patient advocacy and professional groups, individuals in scientific research, and pharmaceutical and biotechnology companies is to create an environment within the government and the general public in which genome research is strongly supported. They provide The TGAC Hotline for members and friends of the Coalition which includes up-to-date information on legislation, up-coming conferences and pertinent resources relating to genetic research.

**The HuGEM Project: Issues in Genetic Privacy and Discrimination, Georgetown University**
**3307 M Street NW, Suite 401**
**Washington, DC 20007 (202) 687-8635 Cost: $15.00**

A 45 minute video of four people affected by genetic disorders who discuss their experiences and concerns about discrimination in insurance and the workplace when privacy and confidentiality are not maintained.

### Internet Resources

**Center for Bioethics at the University of Pennsylvania**
**http://www.med.upenn.edu/~bioethic/**

Maintains the "Ethics and Genetics - A Global Conversation" page which allows individuals to post comments instantly and engage in live conversation about articles on innovative genetic research. Also has a virtual library which contains recent articles on ethical issues regarding genetic technology.

**Exploratorium's Ethical Scenarios Forum (ETHEX)**
**http://www.exploratorium.edu/genepool.ETHEX.html**

ETHEX is designed to offer an opportunity for members of the general public to discuss ethical issues with each other and with professionals in the fields of ethics, genetics, law, theology, sociology and medicine. Individuals can respond to different case scenarios relating to decision-making and genetics, discuss how they would respond and read the responses of others.

*For more information, contact:*

The Arc of the United States
**500 E. Border St., S-300**
**Arlington, Texas 76010**

**(817) 261-6003**
**TDD (817) 277-0553**
**Http://TheArc.org/welcome.html.**

*Produced by The Arc's Human Genome Education Project, Sharon Davis, Ph.D., Principal Investigator and Leigh Ann Reynolds, Project Associate. Funded by the U. S. Department of Energy ELSI Program under Grant No. DE-FG03-96ER62162. Support from DOE does not constitute an endorsement of the views expressed in this publication. October 1996.*

The Arc

# Genetic Issues In Mental Retardation

*A Report on The Arc's Human Genome Education Project* Vol. 1, No. 3

***The Arc's Human Genome Education Project is part of the U.S. Human Genome Project, which is an international effort to identify all the genes within the human body. The goal of The Arc's project is to promote education and discussion of the ethical, legal and social concerns resulting from innovative genetic research. It is funded through the U.S. Department of Energy's ELSI (Ethical, Legal and Social Implications) program.***

## Genetic Testing, Screening and Counseling - An Overview

### Genetic Testing - Harmful or Helpful?

The international Human Genome Project, an effort to map all the genes within our bodies, has greatly expanded our ability to test for the potential presence of certain diseases* that can result in various disorders and conditions, such as mental retardation. This rapid increase in genetic technology is outpacing our ability to develop treatments to correct these diseases and conditions. A growing list of disease-causing genes has been identified, enabling an otherwise healthy individual to know whether or not he or she will develop a disorder or possibly pass a disease gene on to his or her children. This is the first time in history that such specific, predictive genetic information has been available. How will having this information impact society? Do most of us want to know about future genetic information that could change our lives? As a society, we must make decisions we have never had to make before on issues such as the following:

- Who decides who should be screened or tested for genetic disorders?
- Which specific disorders should we screen or test for?
- Who should be providing genetic screening or testing?
- Should we screen or test for disorders even if there is no treatment or cure for the disorder?

A variety of issues have been raised under the areas of prenatal, newborn, carrier and occupational screening, and the testing of children. This report provides an overview of these issues by explaining what genetic testing and screening is, the different types of genetic screening, advantages and disadvantages of genetic testing and other important topics, such as the testing of children and the use of informed consent. The brief discussion on genetic counseling can help individuals decide in choosing whether or not to obtain genetic counseling and how to locate a genetic counselor.

* *Note: Disease is a comprehensive medical term which can include disorders, conditions and illnesses. For this reason, it is used throughout the document to describe the origin of the condition of mental retardation that is directly attributed to genetic inheritance.*

### Key Points on Genetic Testing

- Everyone may not need genetic testing, but those with a history of genetic disorders within the family should consider testing.
- Genetic screening and testing has both positive and negative consequences. It's important to weigh the advantages and disadvantages when considering genetic screening or testing.
- The value of genetic testing depends on several factors: the accuracy of the test, the reliability of the interpretation of the results, the ability to treat the condition and the quality of genetic counseling available.
- Genetic tests can provide medical information that affects the entire family. Testing has implications for future reproductive decisions, usually providing a *probability* of disease, rather than predicting future "diagnoses."
- Reliable genetic tests can predict the chance of having a disease gene with high accuracy. However, not everyone with a disease gene may go on to develop a disease or condition due to possible effects of other genes or environmental factors.
- Informed consent, the communication of information between a patient and health care provider about a genetic test, can be an important component of genetic testing, yet there are no national standards to guide health care providers on how this information should be given.
- Although physicians have not agreed on standards for the testing of children, some experts think that testing should be conducted only when there is clear benefit to the child. Others feel that testing should also be considered if it can benefit other family members.

### Facts on Genetic Testing and Screening

#### What is genetic testing?

Genetic testing is "the use of specific laboratory tests to determine the genetic status of individuals already suspected to be at high risk for a particular genetic condition based on family history or a positive screening test" (Lapham, et.al., 1996). Genetic testing is typically recommended for those individuals who *suspect they may have a disease-causing gene or who may be at an increased risk of developing disease or a condition for reasons other than a family history.*

Pre-symptomatic testing (also referred to as predictive gene testing) is an example of genetic testing. It refers to an individual who is at risk for a genetic disorder (usually because of a family history) but who does not have any symptoms at the time of testing. It is often used to identify single-gene disorders and to determine predisposition to a large number of genetically inherited disorders.

**What is the difference between genetic testing and genetic screening?**

Genetic testing and screening are similar in that both involve the use of laboratory tests to reveal the presence of disease-causing genes. Although genetic screening and testing are essentially the same since they both involve the same medical procedures, the major difference between them can be explained in examining WHY an individual undergoes laboratory testing. If someone desires to be tested due to the possibility that he or she may have a disease gene because a large percentage of people in the same age group or ethnic group are at high risk for having the gene, this individual would need to undergo **genetic screening**. If, however, the individual suspects he or she may have a disease gene as a result of a family member having the gene, this person would need to undergo **genetic testing**.

Screening is often called "population-based" screening since it is used to test those individuals in the population who are at a higher risk for having a disease-gene. For example, people of African American descent are known to be at higher risk for having a gene causing sickle cell disease. On the other hand, genetic testing is used, not to screen a population already at risk, but to "test" individuals for the presence of a specific gene. For example, if a person has a family history of fragile X syndrome, the individual will be tested (as opposed to screened) for the specific gene (FMR1) that causes fragile X syndrome.

**What are the different types of genetic screening?**

Genetic screening is "the testing of apparently healthy people in the population to identify those at increased risk of genetic disease themselves or whose children (including future children) may be at increased risk of disease" (Lapham, et.al., 1996). Genetic screening can include carrier, prenatal and newborn screening.

Carrier screening is often considered by couples who want to have children, but who are concerned that they may "carry" a gene for a certain disorder that has the potential to affect their children.

Prenatal screening is available to those individuals who have a higher risk for passing a disease gene on to the child. It is used to determine the genetic make-up of an unborn child.

Newborn screening identifies biochemical or other inherited conditions in newborns that may result in mental retardation or other complications. Newborn screening is an effective measure in preventing mental retardation. However, only a handful of disorders are screened for since screening all newborns is expensive (The Arc, 1994).

**What is prenatal screening?**

Prenatal screening examines the genetic makeup of a fetus. It is recommended when either parent's side of the family has a history of a genetic disorder or if the mother is over age 34 (since older mothers have a greater chance of having a baby with certain chromosomal disorders, such as Down syndrome) or if there are problems noted through ultrasound (March of Dimes, 1992). Prenatal screening is used to detect certain birth defects or genetic disorders before a baby is born. Examples of genetic disorders that can be detected with prenatal testing include:

- chromosomal abnormalities, such as Down syndrome, trisomy 13 and trisomy 18
- single-gene disorders, such as hemophilia, sickle cell anemia and cystic fibrosis
- neural tube defects, such as spina bifida and anencephaly

Prenatal screening cannot find all genetic abnormalities (since there are only 5,000 known abnormalities out of a total of 100,000 genes in our bodies), and there is some risk involved (as with any medical procedure) depending upon which test is used. Prenatal screening tests currently available include:

- *chorionic villus sampling (CVS)* - usually done at 10 to 12 weeks of pregnancy to obtain a sample of the placenta by passing a plastic tube through the vagina and into the uterus or by passing a needle through the abdomen and into the uterus. This allows doctors to diagnose many of the same conditions as amniocentesis, but earlier in the pregnancy.
- *blood test for alpha-fetoprotein (AFP)* - may be performed at 16 to 18 weeks of pregnancy and is used to indicate the level of AFP, a substance produced by the fetus and passed to the mother's blood.
- *amniocentesis* - may be done at 13 to 18 weeks of pregnancy and is a widely-used procedure of obtaining amniotic fluid from the uterus by using a needle to pass through the abdomen.
- *ultrasound* - usually performed as early as possible in pregnancy, and is a non-invasive procedure that provides a visual image of the fetus (Bowe, 1995).

**How do you know if you should be screened or tested for a genetic disorder?**

Not everyone needs to undergo genetic testing. People who know of a genetic condition within the family are prime candidates since they are susceptible to inheriting a specific disease-causing gene.

*Individuals who could benefit from genetic testing (or diagnostic testing) include:*

- those who are concerned that they may have a genetic or chromosomal disorder because of a specific condition in their families
- couples who already have a child with a genetic disorder, unexplained mental retardation or a birth defect
- women who have had two or more miscarriages or whose baby dies in infancy
- people with unexplained short stature
- people with unusual physical features, especially poor growth or development

*Individuals who could benefit from genetic screening include the following groups of people:*

- women who deliver a child after age 35
- couples who would like testing or information about genetic disorders that occur frequently in their ethnic group

*Others who could benefit from genetic services, such as genetic counseling:*

- pregnant women concerned about the effects of exposure to medication, chemicals or radiation
- couples who are first cousins or other blood relatives (March of Dimes, 1992)

The decision to be tested should always be voluntary and thoughtfully

examined. Individuals should not be forced to make decisions based on pressure from family members, health care providers or others. The possible outcomes (both advantages and disadvantages) of learning what diseases or conditions an individual is at risk of inheriting should be carefully analyzed before making a final decision to undergo genetic testing.

**What are the advantages and disadvantages of genetic testing?**

Genetic testing can cause either a feeling of relief or anxiety, depending on the outcome of the test results. Ultimately, testing provides individuals with an opportunity to seek genetic counseling so that the risk of inheriting a genetic disease may be reduced. Testing can lessen the anxiety of not knowing the possibility of developing a disease and provide a tremendous sense of relief once a definitive test result is given. An individual who chooses to undergo testing has the opportunity to seek medical help, prepare for, and possibly help prevent, a genetically-caused condition (Cho, 1995). Testing can help people to make more informed decisions about their future.

Unfortunately, several negative consequences may result from genetic testing as well. Once a person has tested positive for a disease or condition, he or she risks stigmatization, loss of health or life insurance, loss of employment or educational opportunities and possibly can lose the ability to adopt a child (Geller, et.al, 1996). Privacy of other family members is threatened since, if one family member is tested, this information implies that relatives also could have the disease gene or may have an increased risk for disease.

Another problem of genetic testing is the inability to predict the severity of future disease. The severity of a disorder can vary according to a number of unique factors. Even couples who choose prenatal testing cannot always know in advance the severity of the disability in their child. Also, undesired test results may produce depression and feelings of hopelessness. Relatives may even experience "survivor guilt" which is the feeling of guilt felt by individuals

| What Genetic Professionals Do (Genetic Counselors, Clinical Geneticists, etc.) | How They Do It |
|---|---|
| A family history or pedigree including all medical problems is constructed. | 33 % of people referred for genetic counseling have other genetic issues in their families that need to be addressed. These issues are identified by taking a detailed family history. |
| The family history of genetic disorders and birth defects is analyzed. | Separate the genetic from the non-genetic issues in the family history to avoid unnecessary testing. |
| Genetic counselors assess and interpret the risk for occurrence or recurrence of genetic conditions in the family. | The risk for a genetic condition to occur or recur must be explained with total accuracy. |
| The nature of the condition(s), including the process of inheritance, is carefully discussed. | People need to understand the meaning of a diagnosis (range of severity) and how it is inherited to be able to make a decision about whether they want to be tested and whether they want their unborn child tested. |
| Options available to reduce recurrence risk(s) and specific genetic testing currently available is discussed. | Many options are available to people at risk for a genetic disease, such as carrier screening, adoption, egg/sperm donation and prenatal testing. |
| The risks and benefits of each option is discussed with careful attention being given to the individual's level of understanding. | Each option has risks, benefits, and limitations that individuals need to understand in order to choose the option appropriate for them. |
| Assist in selecting the option appropriate for an individual or family. | Much of the information provided can be confusing. Assisting individuals with decision-making requires good counseling skills and a non-directive approach. |
| Supportive counseling and/or referrals to community resources are provided when appropriate. | Genetic counselors often refer inviduals to other health care professionals or family support groups when necessary. |
| The genetic tests performed are coordinated, when indicated. | Genetic testing is sometimes complex and involves obtaining screening test results and documenting the correct diagnosis. |
| A summary letter documenting the counseling session and an outline of the plan of care is sent to the one tested and the referring physician. | Documenting the counseling session ensures an accurate record for the patient and physician. It becomes a medical-legal document for the patient chart. |

Adapted from *Genetic Consultation/Counseling - The Process* by Beth Balkite, M.S., Certified Genetic Counselor, Genzyme Genetics, August 1996

who have not tested positive for a disease while other family members have (Cho, 1995).

Obtaining a positive test result does not guarantee that a person will become ill and a negative test result cannot completely rule out the possibility of becoming ill. Genetic testing, therefore, often deals in probabilities rather than certainties (NIH, 1995). Physicians can misapply genetic tests now available. Some inexperienced doctors are using genetic testing without fully understanding its consequences (Cotton, 1995). Many genetic tests are being marketed by commercial enterprises without approval from the Food and Drug Administration (FDA), raising questions about the quality of genetic tests and testing procedures (Harvard Women's Health Watch, 1996).

### What is informed consent?

Informed consent is the communication of information between a patient and health care provider about a testing procedure. The purpose of informed consent as it relates to genetic testing is to provide an individual with enough knowledge about the risks and benefits of a genetic test so that a truly informed and educated decision can be made about whether or not to be tested. Informed consent is also important since it limits the scope of testing performed by the health care provider and protects the health care industry in situations involving consumer liability issues.

Health care providers are responsible for providing this vital information in a clear and understandable manner. However, there are no universal standards within the medical field to oversee how this information is communicated and no legal entity which has the responsibility to ensure that enough information is being offered. Some health care providers give a great deal of information, including detailed explanations about testing procedures, while others may provide only minimal information.

Because such variability exists, people considering genetic testing must be aware of what they have a right to ask for and receive throughout the testing process. Some examples include having a right to obtain up-to-date information about each genetic test, to know the benefits and risks of each genetic test, to request a referral for genetic counseling to help decide whether or not to have a genetic test and to receive privacy regarding the test results (Blatt, 1996).

### Should parents be allowed to obtain genetic testing on a child?

Parents have their children undergo genetic testing for several reasons: 1) testing can offer immediate health benefits to the child, such as prevention or early treatment, 2) testing offers no immediate benefits, but can help the child in the future when he or she makes reproductive decisions, 3) testing offers no specific, visible benefits, but the parent or the child requests testing, or 4) testing is done for other family members (Wertz, et.al., 1994).

Often parents want to have their children tested to plan for the future or reduce the anxiety of not knowing. Yet, receiving test results showing that a child does have a disease gene may actually restrict the child's future in many ways. For example, after parents become aware of their child's disease gene, their expectations of the child's abilities and chance of a meaningful life may be substantially lowered. Children could be psychologically damaged by such low expectations, even though treatment may be found to lessen the effects, or eventually cure the disorder. Children, especially younger children, often blame themselves for having a genetic disorder. Such test results may create anxiety within the family, causing the child to suffer abuse or be treated as a scapegoat since the child is the one with the "problem." Other negative consequences of testing children are the possibilities of stigmatization, loss of self-esteem and discrimination by family, employers, insurance companies, educational institutions and others.

Experts feel that allowing children to make important life decisions is risky due to their inability to weigh the future adequately or to realize that their values may change over time. In order to make informed decisions, children need to be able to develop hypotheses and predict future possibilities. But at which age can a child make informed decisions and, therefore, undergo genetic testing? Most children cannot fully comprehend all possible implications of being tested until they reach a certain developmental stage where formal operational thought can be used. They may reach this stage anywhere from age 11 to several years later (Wertz, et.al., 1994).

There are no universally agreed upon standards among physicians for the testing of children. Geneticists and ethicists from around the world recommend that testing be conducted only when there is clear benefit to the child, but others feel testing should be considered if it can benefit other family members.

### What is genetic counseling and how can it help?

Genetic counseling provides important information about the results of a genetic test by translating genetic knowledge into easily understandable and practical information. The interpretation of genetic tests - whether positive, negative or ambiguous - needs to be accurately communicated. Individuals who are considering genetic testing may want to talk with genetic counselors or clinical geneticists who use their knowledge about the basic laws of heredity, family health history (called a pedigree) and results from the genetic testing to estimate the probability that a disorder may recur within the family. Genetic professionals attempt to emotionally and psychologically prepare the individual for receiving positive, negative or unclear test results. Genetic counselors and clinical geneticists provide individuals with relevant information in an unbiased manner about their options after receiving test results so that informed decisions can be made (NIH, 1995).

Genetic professionals typically work in large medical centers or hospitals affiliated with a medical school or university. There are about 300 comprehensive genetic services centers in the United States. Individuals can seek genetic counseling by calling a local hospital associated with a medical school, asking their physician for a referral to a genetic counselor, calling a local chapter of the March of Dimes or by contacting:

- The National Society of Genetic Counselors at 233 Canterbury Drive, Wallingford, PA 19086-6617 (http://members.aol.com/nsgcweb/nsgchome.htm)

- The Alliance for Genetic Support Groups at 1-800-336-4363
- The Council of Regional Networks (CORN) at 1-404-727-1475 (http://www.cc.emory.edu/PEDIATRICS/corn/member/coorlist.htm)

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## Possible Negative Consequences of Genetic Screening

1) Genetic discrimination- People with genetic flaws, not all of which show up as dysfunctions, may be denied life insurance, health insurance, and access to schooling or to jobs.

2) Differential treatment- Employers could hire only those people whose genes indicate they are resistant to the health hazards of the work place, which is a less expensive alternative to making the work place safe for all.

3) Eugenics- Social or political pressure may be applied to people to make childbearing decisions on the basis of genetic information. Mating between those with valued genes may be encouraged while mating between two people with recessive traits that are not valued may be prohibited. Women carrying fetuses with genetic abnormalities may be encouraged to abort.

4) Genetic determinism- Genetic determinism is the belief that behavioral and personality characteristics, such as intelligence or criminal behavior, are mostly a function of genes. Genetic determinism implies a fatalistic attitude toward health and disease. It can be used to justify bigotry and to perpetuate racial or ethnic inequalities. A genetic underclass could be created.

Adapted from *Genetic Testing - Health Care Issues: An Interview with Dr. Neil Holtzman*, Symposium at University of California, San Francisco, 1992.

## Common Myths about Genetic Testing and Genetic Counseling

**Myth:**

If a person has a genetic disorder or has an affected child, usually their chances are high that future children will be affected.

**Truth:**

The recurrence risk depends on the inheritance pattern for that particular disorder in that particular family, and usually ranges from less than 1% to 50%.

**Myth:**

Given that abortion is legal in the United States, many people believe that prenatal diagnosis inevitably means abortion.

**Truth:**

A couple undergoing prenatal diagnosis is never obligated to choose abortion if the result is abnormal. Most of the time, results are normal and parents are reassured and can relax for the remainder of the pregnancy. The availability of prenatal diagnosis has allowed many couples who would otherwise be too afraid to have children to have healthy families.

**Myth:**

A normal chromosome test means that there are no genetic problems in the individual.

**Truth:**

Chromosomes can be seen under the microscope; genes cannot. A normal chromosome test means that the packages of the genes appear to be normal, that is, there is no missing or extra packages of genes. Abnormalities at the level of a gene or a few genes cannot be seen with this test. Most individuals with dominant recessive or X-linked diseases would have normal chromosome tests.

Taken from *Common Myths About Genetics and Genetic Counseling.* The Genetics & Metabolism Department, Children's Medical Center of Dallas.

## What Do You Think?

Once it becomes possible to test quickly and reliably for thousands of genetic conditions, should doctors be expected to perform such tests? Should the doctor be liable for failing to test or for failing to inform parents of every detail of the test result?

Who should counsel patients about what their genetic blueprints mean and how will people react to their particular genetic makeup?

Do health and life insurers who deny policies to people with disease genes have the right to do so?

Should laws be passed to protect people against genetic discrimination?

How can genetic information be kept confidential and how can the discriminatory use of test results be prevented? Since some tests will reveal information about other family members, can the privacy of these relatives be protected?

Do people have the right to choose not to know about their genes? Do mothers have the right to choose not to have their fetuses tested?

Taken from *Genetic Screening and Ethics: An Overview. The Woodrow Wilson Biology Institute*, 1992, David Devore.

### Helpful Resources

Alliance of Genetic Support Groups
35 Wisconsin Circle, Suite 440
Chevy Chase, MD 20815
1-800-336-4363
http://medhlp.netusa.net/www/agsg.html

*Created a helpful 30-minute video on genetic testing called "Genetic Testing Across the Lifespan," and also provides referrals for genetic counseling.*

March of Dimes Birth Defects Foundation
1275 Mamaroneck Ave.
White Plains, NY 10526
1-914-428-7100
http://www.noah.cuny.edu/providers/mod.html

*Provides referrals for genetic counseling and a variety of helpful educational materials related to genetic testing and counseling.*

Understanding Genetic Testing
NCI Cancer Communications Office
Building 31, Room 10A28
Bethesda, MD 20892
1-800-422-6237
http://www.gene.com/ae/AE/AEPC/NIH/index.html

*An easy-to-understand booklet providing an overview of genetics, genetic testing and genetic counseling (Single copies free).*

*For more information, contact:*

The Arc
a national organization on mental retardation


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*Produced by The Arc's Human Genome Education Project, Sharon Davis, Ph.D., Principal Investigator and Leigh Ann Reynolds, Project Associate. Funded by the U. S. Department of Energy ELSI Program under Grant No. DE-FG03-96ER62162. Support from DOE does not constitute an endorsement of the views expressed in this publication. January, 1997*

The Arc

# Genetic Issues In Mental Retardation

*A Report on The Arc's Human Genome Education Project* Vol. 2, No. 1

*The Arc's Human Genome Education Project is part of the U.S. Human Genome Project, which is an international effort to identify all the genes within the human body. The goal of The Arc's project is to promote education and discussion of the ethical, legal and social concerns resulting from innovative genetic research. It is funded through the U.S. Department of Energy's ELSI (Ethical, Legal and Social Implications) program.*

## Protecting Genetic Privacy

### What is genetic privacy and why is it important?

Genetic privacy, in its simplest definition, could be described as the right to decide for yourself what genetic information others can know about you and the right to decide what genetic information you want to know about yourself (Baker, 1997). The growing ability of scientists and researchers to identify genes causing (or contributing to the cause of) certain diseases and conditions threatens the privacy of genetic information in a way that never before required attention.

Without genetic privacy, discrimination based on our genes alone may become commonplace in society. Members of The Arc should become aware of issues surrounding genetic privacy, since many conditions associated with mental retardation are caused by a person's genes. Genetic discrimination has already become pervasive enough to warrant legislation in many states, yet such legislation has fallen short in providing adequate or comprehensive protection of genetic privacy.

### Why has genetic privacy become an issue for The Arc?

The study, definition and "banking" of human genes, heavily influenced by the research of the Human Genome Project (HGP), is quickly becoming a great concern to those who have any defective genes within their bodies (and that means all of us). The Human Genome Project is an effort among scientists worldwide to identify all 80,000 to 100,000 genes within the human body. This goal is being reached faster than originally expected, which means genetic information is being discovered before society is ready to know what to do with the information. Some fear the advance in research made by the HGP will be used to deny health insurance to more and more people, such as individuals with mental retardation and their family members. Hundreds of DNA tests will become available early in the next century, so we must prepare ourselves by learning how to protect genetic information.

### Why is genetic privacy a concern for individuals and families affected by mental retardation?

A person's genes can tell a lot about that person. Employers, insurance companies, educational institutions, adoptive agencies and others can find out what conditions or diseases a person may have or be predisposed to getting. However, genetic test results can be misinterpreted by such organizations who are unfamiliar with genetics and the correct interpretation of the results of such tests. Having a gene for a certain condition does not necessarily mean the individual will ever show symptoms of the condition. This is a fact insurance companies and prospective employers may not know and thus incorrectly assume the presence of a condition.

Also, federal law does not require those who obtain genetic information to protect it. Although some states have banned genetic discrimination, the chance that a person will be discriminated against based solely on his or her genetic make-up remains a high possibility.

### KEY POINTS ON GENETIC PRIVACY

- Many people do not know how to protect their genetic information, or realize that the privacy of their genetic information needs protection.
- A person's genes have the potential to tell a lot about that person, but genetic test results can be misinterpreted by insurance companies and prospective employers.
- Genetic information is significantly different from other medical information since genetic testing often involves other family members who may or may not want to know or do not want to provide genetic information.
- Genetic databanks (or DNA databanks) are computerized databases that store records obtained through genetic testing. Once genetic information is obtained, those receiving the information are under no obligation to protect it.
- Fourteen states have enacted laws that prohibit using genetic data in insurance underwriting, but such laws do not provide adequate protection of genetic privacy.
- Protecting the privacy of genetic information isn't easy, but there are steps one can take to obtain the most protection possible.

EC 306225

For example, some people may be discriminated against because they carry the gene that causes fragile X syndrome, the most common inherited cause of mental retardation. Twenty percent of people with this gene will never display any form of mental retardation. Yet, since they carry the fragile X gene, they could be treated as though they had mental retardation even though they do not (Boyle, 1995).

The importance of protecting privacy is not new, but protecting *genetic privacy* is raising concern and has its own unique set of issues. Although there is currently no DNA-based test for newborn screening in the United States, within the next ten years it may be possible for such testing to reveal disease genes (or genetic mutations). Individuals who may never be affected by a disease gene, but only be a carrier for the genetic condition, could face a future of discrimination due to the increased use of genetic testing in society. Without laws in place to protect genetic information, the possibility of being discriminated against based on genetic make-up alone is one of the major concerns related to privacy.

In addition to these problems, genetic testing provides highly sensitive health-related information that, while some individuals feel is important to know, others choose not to know. Genetic information is significantly different from other medical information since genetic testing often involves other family members who may or may not want to know or do not want to provide genetic information.

## How is genetic information obtained?

Genetic information is obtained through the study of our body cells. Genes are the basic units of heredity that are passed down from one generation to the next. Genes are made up of a body chemical called DNA (deoxyribonucleic acid). Our DNA can be obtained through several different ways, such as from saliva, hair, fingernails, blood, semen, skin and nail clippings. Virtually all clinical DNA testing uses blood as the method of obtaining a sample of DNA.

## Why is our genetic information being stored?

Genetic information is routinely stored within hospital data banks. It's collected with the goal of improving patient care or to reduce the likelihood of disease (Council for Responsible Genetics, 1995). Our genetic information provides a way to easily identify who we are and certain information about us. Other reasons why our genetic information is being stored are to:

- Conduct research

In mapping our genes, scientists hope to prevent future disease and discover treatments and cures for diseases and conditions, such as mental retardation.

- Establish identity of suspects

DNA is being used by lawyers as strong evidence to establish the identity of individuals suspected of committing crimes. It has been used in thousands of cases in the U.S. and other countries.

- Prove fatherhood

In order to prove paternity (whether or not a man is the father of a child), a blood sample is often taken in order to extract DNA. In divorce proceedings, this is often used to determine who is responsible for child support payments and who will get custody of children.

- Identify bodies

DNA can be taken from bodies that may be difficult to identify due to severe damage of the body, such as from fire or military combat. In the latter application, there is hope that never again will there be an unknown soldier.

- Study human evolution

Scientists are collecting DNA samples from skeletons of humans who lived thousands of years ago in order to better understand the process of our evolution (Baker, 1997).

DNA-based tests are also used for:

- prenatal testing (for some conditions)
- identification of a carrier for a specific condition
- diagnostic testing
- pre-symptomatic testing
- risk-oriented or susceptibility testing, e.g., such as determining susceptibility to inheriting breast cancer (Kotval, 1994).

## What are genetic databanks?

Genetic databanks (sometimes referred to as DNA databanks) are computerized databases that store records obtained through genetic testing. Gene databanks are used for several different purposes, but predominantly for forensic purposes. Genetic information may be obtained directly from a crime scene through blood (in the case of murder or other violent crimes) or semen (in the case of rape). Other genetic information stored includes actual biological samples from genetic tests and newborn blood samples taken to test for PKU and other genetic conditions.

## Why is The Arc concerned about DNA Databanking?

There are many situations where people must provide personal information. Several include applying for a job, life or health insurance, credit or financial aid and benefits from the government. As the use of genetic testing grows, insurers and employers will want to obtain test results in order to determine the health status of the applicant or

employee. Such information can be highly sensitive and personal. Once this information is provided, the companies/institutions/individuals are under no obligation by law to protect it. In fact, "there is no law which says that a blood sample collected for one kind of DNA testing can't be used for another purpose" (Baker, 1997). The law also does not give individuals the right to check their DNA file to see if the information is correct.

Genetic information may be used by people other than medical professionals. For example, insurance companies or employers may want to "weed out" applicants or possible new hires whose genetic information is considered undesirable. Although the definition of desirable or undesirable genetic information remains somewhat ambiguous, genes causing mental retardation are susceptible to being labeled "undesirable" which can negatively impact the individual and family members of someone with this disability. Although some types of medical information, such as HIV status, may be kept in separate files so that fewer people can see them, if a "release of medical records" form is signed, insurers are entitled to see everything, including separate files (Wertz, 1997).

This lack of protection of genetic privacy raises a variety of ethical issues, especially in respect to genetic discrimination. Genetic discrimination in health insurance and employment is common since an individual's medical information is often requested by non-medical personnel, such as insurance companies and employers. A survey conducted by the University of Illinois found that 50% of companies use prospective employee's medical records when making employment-related decisions, and 19% of these individuals are not told that their medical records are being considered as a factor in the hiring process (Alpert, 1993).

Another concern is that as medical records become more centralized and computerized, they will more easily be made available to corporations, social service agencies and others, similar to the wide availability of credit histories (Alper and Natowicz, 1993).

### Are there any laws to protect genetic privacy?

Genetic privacy legislation covers a wide array of issues, such as informed consent, privacy and confidentiality, as well as genetic discrimination in health insurance and employment. A few states have some legislative protection of genetic privacy, mostly in the form of genetic nondiscrimination laws. Fourteen states have enacted laws that prohibit using genetic data in insurance underwriting, but such laws fall short of providing adequate or comprehensive protection of genetic privacy (Council for Responsible Genetics, 1997). With support from the Department of Energy's ELSI (Ethical, Legal and Social Implications) program, Boston University School of Public Health developed a "Model Privacy Act" based on the premise that genetic information is different from other types of information in ways that require special protection (Annas, et.al., 1995).

Privacy legislation generally fails to address whether or not data obtained for one purpose can be used for another unrelated purpose (also referred to as secondary uses of information). Genetic information is especially vulnerable to this type of misuse. Genetic test results obtained to verify the risk of disease may have originally been obtained only for that purpose. However, such information may serve a number of secondary purposes for insurance companies and employers who can use the information to their advantage.

A national survey revealed state statutes are often silent about the degree of privacy protection provided, allow weaker protection to certain types of health information, or give health officials broad discretion to disseminate personal health information (Gostin, et.al., 1996). Due to the wide variability that exists between state law regarding privacy, federal law has been proposed that, some suggest, should preempt state law. However, depending on the strength of yet to be enacted federal law, it could weaken existing state law (Marwick, 1996).

In 1996, several bills calling for uniform national standards in privacy law were introduced in Congress, but none were adopted. While it is expected that further activity will occur, most privacy legislation activity is taking place at the state level.

### Aren't medical records private?

Anyone who has ever filled out an application for individual life, health or disability insurance should have filled out an "MIB Notice" within their application. Through the Medical Information Bureau (MIB), insurance companies have access to the medical records of people who have applied for insurance. The MIB, a private, non-profit corporation located in Massachusetts, manages a computerized data bank of information to provide insurance companies with medical and certain non-medical information about applicants for insurance. Originally created to prevent insurance fraud, the MIB holds medical information for 10 to 20 million Americans (Geller, et.al., 1996).

If an insurance applicant has a condition significant to health or longevity, such information must be provided by insurance companies to the MIB. Some of the information routinely reported include height and weight, blood pressure, EKG readings and x-rays if such information is considered significant to health and longevity. Non-medical information that could affect insurability can also be reported,

such as adverse driving record, participation in hazardous sports and aviation activity.

Consent from the individual must be given in order to establish an MIB file or to allow a data bank search. However, if the applicant decides not to give consent, insurance companies may automatically deny coverage (Council for Responsible Genetics, 1995).

## How can I attempt to protect the privacy of my genetic information?

Protecting the privacy of genetic information is challenging and difficult. For example, if an applicant for health insurance responds honestly to the question of whether or not he or she has a genetic or hereditary illness, this could eliminate any chance of obtaining health insurance. If genetic information is withheld or concealed from the insurance company, does this mean that coverage for associated problems would be denied? If one declines to answer truthfully does this mean that insurance will be denied? Either way, whether a person decides to respond truthfully or decides to not respond at all, coverage can be denied.

Until adequate legal protection is available, the following suggestions should be considered to protect your genetic information.

To attempt to keep genetic information as private as possible, physicians and other medical providers should be instructed in writing that they are not allowed to disclose your genetic information to anyone without prior verbal and/or written consent.

Whenever you apply for insurance, note if the application says, "if you have been advised of" any genetic or hereditary illnesses, conditions or diseases. If yes, and you sign a completed application, the insurance company can send a copy of your application to the MIB, which means all future insurers will have access to your genetic information (Morelli, 1992).

If MIB has a file on you, you can obtain a copy of the report to determine if anything in the file is incorrect and change it if it's wrong. The information within the report is translated from code to reveal the specific conditions. Medical conditions are reported by using one or more of about 210 codes.

You can file a statement of dispute if you disagree with information in the file. If the information was accurate when reported, but has changed and is no longer accurate (for example, a medical condition that has improved), a "statement of additional information" can be submitted describing the improvement or correction. To determine if you have a file or to request a copy of your medical file, contact the MIB at 617-426-3660 (P.O. Box 105, Essex Station, Boston, MA 02112). Cost is $8.00.

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## Fragile X Syndrome

### Introduction

Many forms of mental retardation are assumed to result from a disrupted or abnormal gene, but only a small fraction have been identified. Some genetic conditions, such as Down syndrome, are spontaneous abnormalities, whereas others are inherited, transmitted by carriers or affected individuals from one generation to another. Of the known genetic causes of mental retardation, fragile X syndrome is currently considered the leading inherited cause, with an incidence between 1:2,500 and 1:4,000.

### What is Fragile X Syndrome?

Fragile X syndrome is a single gene disorder located on the X chromosome. Understanding the basics of fragile X syndrome requires an understanding of how genes themselves are constructed and what they do.

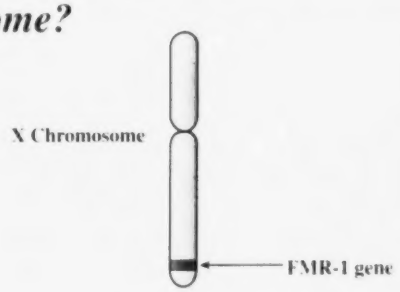
Genes are made up of DNA, which provides the blueprint for life. This blueprint is a code containing four letters (C, G, A, T), abbreviations for four different nucleotides (cytosine, guanine, adenine, and thymine). Nucleotides are the essential building blocks which make DNA. The letters and the sequences in which they are arranged construct the messages which lead the body to produce key proteins.

Fragile X syndrome results from a *mutation* (a change in the typical DNA sequence) known as a trinucleotide repeat expansion. This means that a series of three particular nucleotides (CGG) in the DNA is greatly expanded beyond its normal size, disrupting the normal messages that need to be sent. This fact was discovered in 1991 by several teams of researchers studying the X chromosome.

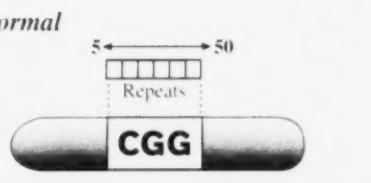
In the FMR-1 gene located on the X chromosome, most individuals have a CGG trinucleotide repeat that occurs between 5 and 50 times, the average being around 30. These individuals are *normal* with respect to fragile X syndrome, and usually carry no

### *What is Fragile X Syndrome?*

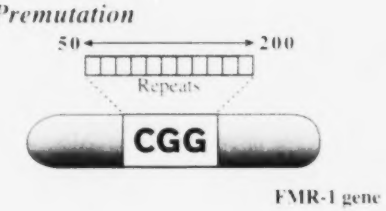
1 The FMR-1 gene is located on the X chromosome. This gene is responsible for instructing the cell to make FMRP, a protein assumed to be essential for normal brain functioning.



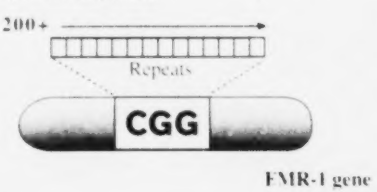

2 The genetic code for the FMR-1 gene usually contains a limited repetition of CGG sequences. The *normal* range is 5-50 repeats.




3 Some people have an expanded number of CGG repeats. When the number of CGG repeats is between 50 and 200, the individual is a *premutation carrier* of fragile X syndrome. Carriers are not usually affected by fragile X syndrome, but they are at risk of having affected children.




4 If the number of repeats exceeds 200, usually this disrupts the code and prevents the production of the FMR protein. These individuals have the *full mutation* and usually are affected by fragile X syndrome.



risk of transmitting it, although the 40-60 repeat range is sometimes considered a "gray zone" which may or may not be unstable (have a risk of expanding). Some individuals have CGG sequences that are repeated in the range of about 50 to about 200. These individuals are generally referred to as *premutation carriers*. This means that they carry the syndrome and can transmit it to their children. Premutation carriers, however, are not usually affected by fragile X syndrome. When the number of CGG repeats expands beyond 200, the individual usually has the *full mutation*. This means that they have fragile X syndrome and will experience the impairments and delays associated with the syndrome.

## How is Fragile X Syndrome Detected?

Fragile X syndrome is detected through a DNA analysis that almost always requires drawing blood. The technique for identifying fragile X syndrome is a specialized process and not all genetic labs have this capability. For those that do have this capability, the procedure is virtually 100 percent reliable. Prenatal identification is also possible. However, it is impossible to determine how severely affected the child might be based on this procedure.

## How is Fragile X Syndrome Inherited?

Fragile X syndrome is carried on the X chromosome. Since both males (XY) and females (XX) each have at least one X chromosome, both can be carriers or have the syndrome. If a father is a carrier, he can only pass the gene defect to his daughters, since he transmits a Y chromosome to his sons. All of his daughters will inherit the gene, and as far as is known, transmission from father to daughter only occurs in a premutation state. In other words, if a daughter inherits the gene from her father, she will have the premutation, not the full mutation. Interestingly, this happens even if the father has the full mutation, as the sperm of males with the full mutation has been shown to be in the premutation phase.

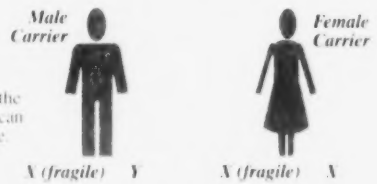
If a mother is the carrier, she can pass the gene defect to either sons or daughters, since she contributes an X chromosome to each. Children of carrier mothers have a 50 percent chance of inheriting the gene, since the mother has two Xs to give and only one is affected. It is through mothers that the gene can expand from the premutation to the full mutation. So, a carrier mother can have normal children, children with the premutation, or children with the full mutation.

The chances of expansion into the full mutation increase with successive generations. Thus the gene could be passed down in the premutation phase for several generations without anyone suspecting that the family has a genetic disorder that ultimately will lead to mental retardation or other developmental disabilities.

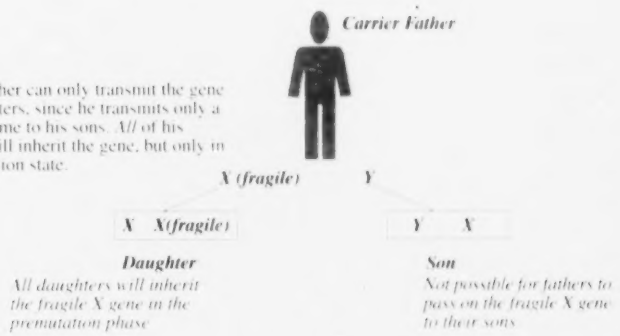
### *How is Fragile X Syndrome Inherited?*

1 For a child to inherit fragile X syndrome, one parent must be a *carrier*.

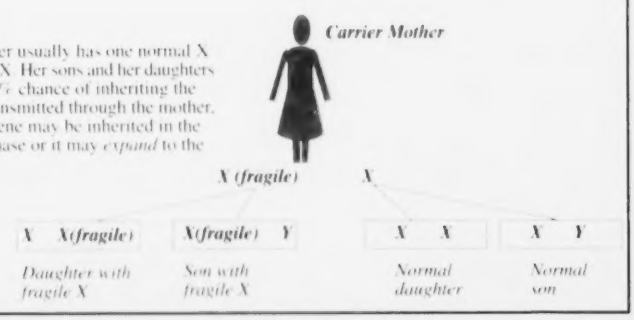
2 Since fragile X syndrome is carried on the X chromosome, both males and females can be carriers and can inherit the syndrome.




3 A carrier father can only transmit the gene to his daughters, since he transmits only a Y chromosome to his sons. *All* of his daughters will inherit the gene, but only in the premutation state.


Carrier Father
X (fragile) Y
X X(fragile)
Y X
Daughter
All daughters will inherit the fragile X gene in the premutation phase
Son
Not possible for fathers to pass on the fragile X gene to their sons

4 A carrier mother usually has one normal X and one fragile X. Her sons and her daughters each have a 50% chance of inheriting the gene. When transmitted through the mother, the fragile X gene may be inherited in the premutation phase or it may *expand* to the full mutation.



## What Are the Effects of Fragile X Syndrome?

The biological effect of this expansion of CGG repeats is to shut down the production of the FMR-1 protein. The function of this protein is currently the subject of intense study, but it is clear that it is essential for normal brain function. Loss of the protein affects overall development, patterns of behavior, and physical features. These effects are different for males and females.

Effects on males. Males with the full mutation are more severely affected than females. Most will have mental retardation, ranging from mild to severe. Delays are usually evident in all developmental domains, although cognitive and communication skills are likely to be most affected. They may seem shy and often have problems with social skills and attention. One common feature that has been described is hyperarousal, which means that they can easily become overstimulated and may appear to overreact to changes in environment, routines, or expectations. Lack of eye contact is frequently observed.

Males also have several distinguishing physical features. They often have large ears, loose joints and muscles, and an elongated face. After puberty males usually have testicles which are significantly larger than usual.

Effects on females. Females generally have more mild impairments. Females have two Xs, but in each cell only one becomes activated, a process that appears to be random. On average, therefore, about half of a female's cells will use the normal X (from the non-carrier parent) and half will use the fragile X. About one-third of females with the full mutation will have normal development, about one-third will exhibit learning disabilities, and about one-third will have mental retardation. They may also be shy and have mild social problems.

## What Are Some Major Issues Facing Parents and Professionals Today?

Now that researchers know the genetic basis for fragile X syndrome, much work is being invested in understanding the function of the FMR-1 protein. Behavioral scientists are working to describe in more detail the specific kinds of learning challenges faced by persons with fragile X syndrome and to identify the kinds of educational and therapeutic strategies most likely to be successful. In the meantime, families and practitioners are trying to address a number of challenges:

Promoting early identification. Most cases of Down syndrome are identified at birth on the basis of physical features. However, fragile X syndrome is not at all obvious at birth. Usually parents begin to notice behavioral problems (inability to cuddle, lack of regular routines, fussiness) or delayed attainment of developmental milestones (walking, talking). Sometimes these signs are subtle, and it may take a long time for a physician or other professional to acknowledge that a problem exists. Even then the child may not be referred for genetic testing. As a result, many cases of fragile X syndrome remain undiagnosed or are diagnosed later than most parents would prefer. Physicians need to be better informed about fragile X syndrome, and more research is needed that will help identify early signs of fragile X syndrome.

Supporting extended families. Often fragile X syndrome is identified in families where there was no prior knowledge of its existence. Because it is an inherited disorder, other family members inevitably become involved and may be identified as carriers or as having the disorder. The process of informing other family members and helping extended family members cope with this unexpected information is challenging and one for which outside support can be especially helpful.

Determining medical treatments. There is no cure for fragile X syndrome. Many researchers are studying gene therapy in hopes of ultimately identifying ways to correct genetic disorders. However, this process has yet to be successful with any disease, and since brain disorders pose unique challenges, a cure is unlikely in the near future. Medical interventions are thus primarily limited to medications. A number of medications have been identified as being helpful in addressing problems related to anxiety, attention, and activity. However, there is not a standard prescription regimen and usually several drugs must be tried independently or in combination with each other before an effective treatment is identified.

Determining educational and therapeutic treatments. Most persons with fragile X syndrome need special education and therapeutic services. Unfortunately, little research has systematically examined the effectiveness of various treatments or interventions. General suggestions include designing a structured, predictable environment, eliminating distractions, allowing for periods of rest and escape from demands, and clear communication of expectations and feedback. Speech and language therapy as well as occupational therapy are recommended for most affected individuals.

Differentiating fragile X syndrome and autism. Males with fragile X syndrome may display autistic-like behaviors such as hand-flapping or social avoidance, and many are initially referred for an autism evaluation. Research shows that while fragile X syndrome is not a major cause of autism, about 15 percent of persons with fragile X syndrome may meet diagnostic criteria for autism at some point in their lives. However, the basis for autistic-like behavior may be different for the two populations and more research is needed on the implications for treatment.

## Conclusion

Although fragile X syndrome is the most commonly occurring known inherited cause of mental retardation, it accounts for only a small portion of all the cases of mental retardation. However, it is an interesting disorder from a genetic perspective and knowledge of the mechanism by which it is caused may help our understanding of other genetic causes as well. The syndrome has implications both for affected individuals and for their families. Research to date has focused primarily on the genetic aspects of fragile X syndrome. Effort now needs to be invested in educational, psychological, and therapeutic intervention studies to identify ways to maximize development, adaptive functioning, and quality of life.

*This report was prepared by Don Bailey, Ph.D. Don is Director of the Frank Porter Graham Child Development Center of the University of North Carolina at Chapel Hill, where he and his colleagues are conducting several studies of fragile X syndrome during the early childhood years. Thanks to Dr. Deborah Hatton (UNC-CH) and Dr. David Nelson (Baylor College of Medicine) for their feedback on the report. The graphics were produced by Brady Fowler of the FPG Center.*

## Fragile X Syndrome Resources

### Books and Pamphlets

*The Fragile X Child.* (1992). B. B. Schopmeyer & F. Lowe ($39.95 plus $5.25 shipping). Singular Publishing Group, 4284 41st St., San Diego, CA 92105-1197 (1-800-521-8545)

*Educating Boys with Fragile X Syndrome.* (1994). G. A. Spiridigliozzi, A. M Lachiewicz, C. S., MacMurdo, A. D. Vizoso, S. M. O'Donnell, A. McConkie-Rosell, & D. J. Burgess ($10, checks to DUMC) (919-684-5513). Gail Spiridigliozzi, Child Development Unit Box 3364, Duke University Medical Center, Durham, NC 27710

*Behavior and Development in Fragile X Syndrome.* (1994). E. M. Dykens, R. M. Hodapp, & J. F. Leckman. Sage Publications, 2455 Teller Road, Thousand Oaks, CA 91320

*A Parent's Guide to Drug Treatment of Fragile X Syndrome.* (1995). Michael R. Trantaglia. ($25). FRAXA Research Foundation, P.O. Box 935, West Newbury, MA 01985 (508-462-1990)

*Fragile X Syndrome: Diagnosis, Treatment, and Research, Second Edition.* (1996). R. J. Hagerman & A. Cronister ($35). Johns Hopkins University Press, 2715 N. Charles St., Baltimore, MD 21218-4319 (410-516-6956)

*Fragile: Handle with Care--Understanding Fragile X Syndrome.* (1996). M. Braden ($25). Avanta Publishing Company, 75 South Elliott St., P.O. Box 17023, Chapel Hill, NC 27514 (919-967-0322)

### Newsletter

*National Fragile X Advocate.* Pam Brode, Editor-in-Chief. One year subscription for individuals/nonprofits (4 issues), $36. Avanta Publishing Company, P.O. Box 17023, Chapel Hill, NC 27516-1702. (919-967-0322/800-434-0322)

Email address: pbrode@nando.net

### Resource Centers, Agencies

National Fragile X Foundation, 1441 York St., Suite 215, Denver, CO 80206 (1-800-688-8765/303-333-6155) Fax: 303-333-4369,

Website: www.fragilex.org

Email address: natlfx@aol.com

FRAXA, P.O. Box 935, West Newbury, MA 01985-0935 (508-462-1990/Fax: 508-463-9985) Email address: fraxa@seacoast.com

Web site: http://www.fraxa.org

Listserve: Instructions to join found on FRAXA website.

### Articles

Hagerman, R. J. (1997). Fragile X syndrome: Meeting the challenges of diagnosis and care. *Contemporary Pediatrics*, 14(3), pp. 31-59.

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The Arc®

# Genetic Issues In Mental Retardation

*A Report on The Arc's Human Genome Education Project* Vol. 2, No. 3

*The Arc's Human Genome Education Project is part of the U.S. Human Genome Project, which is an international effort to identify all the genes within the human body. The goal of The Arc's project is to promote education and discussion of the ethical, legal and social concerns resulting from innovative genetic research. It is funded through the U.S. Department of Energy's ELSI (Ethical, Legal and Social Implications) program.*

# Gene Therapy and Mental Retardation

## What Is Gene Therapy?

Gene therapy is an experimental treatment in which normal genes are introduced into the body's cells in order to correct or modify the function of the cell which is not working. The initial purpose of gene therapy was to treat hereditary diseases by adding good genes to function for missing or defective genes. Researchers soon discovered that genes could also be introduced into cells to help patients fight disease.

There are two kinds of gene therapy. Somatic cell gene therapy is directed at treating the somatic cells (the non-sex cells) which are all the body cells, except the reproductive cells. Somatic cell gene therapy is generally viewed as a conventional medical therapy that is not a major departure from established medical practice (Morsy et al, 1993). It would result in correcting a genetic defect only in the non-sex cells of the person being treated.

In contrast, germ line gene therapy would treat cells of the reproductive tissues of a patient, the germ or sex cells, in such a way that the disorder would also be corrected in any offspring of the individual (Anderson, 1985). (The sex cells are called germ cells and include the egg and sperm.) Because future generations are affected, germ line gene therapy is the focus of concern and discussion regarding whether it is an ethical approach to treating genetic disorders. The federal government does not fund this type of gene therapy at this time.

### Key Points

- Gene therapy is an experimental treatment in which normal genes are introduced into the body's cells in order to correct or modify the function of the cell.
- No one has yet been "cured" of a genetic condition by gene therapy, although it is considered a promising tool for treating single gene defects causing mental retardation.
- The potential availability of gene therapy raises a variety of ethical issues including acceptance of gene therapy as an appropriate means to treat mental retardation, eugenics, fair allocation of resources to gene therapy research, genetic enhancement of cognitive abilities and participation of infants and children in research.
- Families must be informed about gene therapy ethical issues in order to express their views and personal experiences to policy-makers.

## Status of Gene Therapy

More than 250 research trials are under way using somatic cell gene therapy (Lyon, 1997). Many studies have involved treatment of cancer; others involve inherited disorders like cystic fibrosis. While researchers are learning a lot about how to conduct gene therapy, there has not yet been a cure for any of the conditions being treated. Most studies have only involved a small number of patients to test the possibilities of the transfer of genes into body cells and to evaluate the effects of this treatment.

Members of a National Institutes of Health panel that investigated the status of research on gene therapy believe gene therapy holds great promise. However, the panel noted the public's mistaken and widespread perception that gene therapy is further developed and more successful than it actually is. The panel expressed concern that patients, their families and health providers may make unwise decisions regarding treatment alternatives, believing cures are "just around the corner" (Orkin and Motulsky, 1995.) Scientists disagree on how many years of development are needed before gene therapy becomes a proven treatment, but most of them in the field believe gene therapy is on track to be the "most powerful curative and diagnostic tool ever" (Lyon, 1997).

## Basic Gene Therapy Techniques

In gene therapy, healthy copies of genes are given to someone whose own versions are faulty or missing. There are two basic methods for doing this. The *ex vivo* method removes selected cells from the patient's body, introduces the normal copy of the defective gene (therapeutic gene) into these cells and then returns the cells to the body. The *in vivo* method inserts the therapeutic genes directly into the targeted

body cells generally using a type of virus as a carrier (Batshaw, 1997).

There are many challenges to accomplishing gene therapy. One hurdle is to get the therapeutic genes into cells without causing harm to the body. Researchers also need to control the specific types of cells a therapeutic gene enters. For example, if the condition affects liver function, the therapeutic genes will be targeted to reach the liver cells. Once the genes are inside the cell, scientists would like to be able to control the level of activity needed to correct the problem. This means the new gene must function normally in the cell (Orkin and Motulsky, 1995).

## Can Gene Therapy Be Used to Treat or Cure Mental Retardation?

At this time, the most promising use of gene therapy is to treat single gene defects causing significant disability that cannot be treated satisfactorily by other approaches (Moser, 1995). Gene therapy studies to test the safety and the effects of the treatment have begun in a number of genetic disorders causing mental retardation, including phenylketonuria (PKU), Gaucher Disease, Lesch-Nyhan syndrome, urea cycle disorders and Duchenne muscular dystrophy. (See box).

The current approaches to gene therapy cannot be used to treat the most common chromosomal abnormality that causes mental retardation, Down syndrome. Even though we know that an extra chromosome 21 causes Down syndrome, scientists have not yet identified the specific number and location of genes involved. The gene causing fragile X syndrome, another common genetic cause of mental retardation, has been identified. At some time in the future, it may become possible to apply gene therapy to fragile X. However, much more knowledge is needed about the function and control of the fragile X gene before gene therapy experiments are undertaken (Moser, 1995).

## Conditions Undergoing Gene Therapy Research

### Lesch-Nyhan Syndrome (LNS)

Lesch-Nyhan syndrome is an X-linked metabolic disorder caused by deficiency of hypoxanthine-guanine phosphoribosyltransferese (HPRT). It is characterized by excess uric acid in the blood which results in symptoms including, writhing movements, communication deficits, mental retardation and involuntary self-injurious behavior. Most males with the disorder have to be restrained to keep from inflicting severe damage to themselves.

LNS is considered suitable for gene transfer techniques because the genetic defect is well understood. There are also mice with HPRT deficiency suitable for testing gene transfer carriers. The major impediment to gene therapy for LNS is the gap in knowledge about causes of the various neurological defects, including communicative defects, mental retardation and self-injurious behavior (Friedmann, 1995).

### Phenylketonuria (PKU)

PKU is an autosomal recessive disorder caused by a deficiency of hepatic phenylalanine hydroxylase which is usually diagnosed at birth through newborn screening programs. A diet low in phenylalanine will prevent the profound, irreversible mental retardation characteristic of the disease. However, individuals on the diet may still have some cognitive impairments or behavioral disturbances.

Animal models have been useful for evaluating the effectiveness of different gene therapy treatments. As yet, no effective mechanism for inserting the gene and for obtaining therapeutic results over time has been found. However, research continues, and scientists are optimistic that the challenges will be solved (Fang, Eisensmith and Savio, 1995).

### Ornithine Carbamoyltransferase (OTC) Deficiency and Other Urea Cycle Disorders

Urea cycle disorders are inborn errors of metabolism caused by a deficiency of one of the enzymes needed for the synthesis of urea from ammonia. The deficiencies cause an excess of ammonia in the blood and body tissues. Many children with this condition do not survive the newborn period and those that do have a high incidence of mental retardation and other developmental disabilities.

Gene therapy studies have focused on OTC deficiency in part because there are mouse models of this disease and in part because this disease is particularly resistant to current therapies. Different approaches to gene therapy are being developed for treatment with the prospect of clinical trials beginning soon (Robinson, Batshaw, Ye, and Wilson, 1995).

### Duchenne Muscular Dystrophy (DMD)

Duchenne muscular dystrophy is a wasting disease of muscle caused by mutations in a single gene on the X chromosome. Because no effective treatment is available, the disease is inevitably fatal by the third decade of life. About one third of all males with DMD have mental retardation.

Gene transfer technology focuses on correcting the biochemical defect (dystrophin-deficiency) in muscle fibers of DMD patients which somehow is likely related to the mental retardation as well. Experimental studies in mice have shown that dystrophin gene transfer to skeletal muscle is possible and that its efficiency in the mouse may be high. The next stage of inquiry will use dystrophic dogs in order to answer questions related to efficiency, dosage, route of administration and safety limits (Dunckley, Piper, and Dickson, 1995).

### Gaucher Disease

Gaucher disease is an autosomal recessive disorder that is the result of inherited deficiency of the enzyme glucocerebrosidase. The enzyme deficiency can result in massive enlargement of the liver and spleen, decreased numbers of red blood cells and platelets and skeletal deterioration. There are three types; Type 1 is the mildest (and most common), while Types 2 and 3 are more serious and include mental retardation.

Gene therapy research has focused on Type 2 Gaucher disease which is rapidly progressive and usually leads to death by two years of age. Because no naturally occurring animal model is available, researchers first developed a Type 2 Gaucher mouse. These mice have provided new insights into the mechanisms that result in the most severe forms of Gaucher disease. They will be valuable for testing gene therapy strategies for Gaucher disease (McKinney et al., 1995).

# Ethical Issues Related to Gene Therapy

Many people are concerned about the ethics and possible misuse of gene therapy. Gene therapy studies in this country are strictly regulated by the federal government and national review panels. The government has been very concerned about ethical questions and has sponsored research studies and national forums to investigate the issues. The pros and cons of both somatic cell and germ line gene therapy have been, and continue to be, debated. This section reviews some of the ethical issues related to gene therapy in general and specific issues that may affect families with a genetic mental retardation condition.

## Acceptance of Gene Therapy as Appropriate Medical Treatment

Scientists and ethicists have been formally debating the scientific and ethical issues raised by the prospect of human gene therapy since the late 1960s. These discussions have largely helped resolve the uncertainties regarding the ethical and public policy aspects of somatic cell gene therapy. The arguments for the benefits of this type of gene therapy are considered to outweigh arguments opposing it, and it is generally viewed as an acceptable medical intervention (Morsy et al, 1993). This does not mean that there are not differing views, for a few individuals oppose any type of gene therapy (Coutts, 1991). Many people believe that gene therapy should be reserved for treating specific disorders that cause great suffering, mental disability, pain and early death. Others have not ruled out gene therapy to enhance human traits not related to disease, such as cognitive ability.

The issues related to germ line gene therapy are still being debated, even though it has the potential to cure genetic disorders in future generations. While some believe it should be banned, others disagree with that view. Suggested guidelines for germ line gene therapy treatment include: 1) somatic cell gene therapy must be established as safe and effective prior to attempting germ line gene therapy; 2) animal studies must demonstrate safety and effectiveness of germ line therapy; and 3) a public process must be used to gain approval of the procedure (Fletcher, 1995). Some of the arguments for and against each type of gene therapy are presented in Table 1 (Coutts, 1991).

### Table 1

### ARGUMENTS FOR AND AGAINST GENE THERAPY

#### Somatic Cell Gene Therapy

| Arguments for | Arguments Against |
|---|---|
| Has potential for treating desperately ill patients or preventing the onset of severe illness in an individual. | There is potential for harmful abuse if distinction is not made between good and bad uses of gene therapy. |
| Obligated to patients and to future generations to treat their severe illnesses or genetic conditions if possible. | Difficult to monitor long-term effects. |
| Can make individuals functional, employable. | Individuals' reproductive liberties and privacy interests will be pitted against the interest of insurance companies or society in not bearing the financial burden of caring for children with serious genetic defects. |
| | If only those who can afford gene therapy receive it, the distribution of desirable biological traits will widen the differences among various socioeconomic and ethnic groups. |
| | Many candidates are children who are too young to understand the ramifications of gene therapy treatment. |

#### Germ Line Gene Therapy

| Arguments for | Arguments Against |
|---|---|
| Offers a true "cure," not just treating symptoms in one individual. | Too much scientific uncertainty and clinical risks; long term effects are unknown. |
| May be the only effective way of treating some genetic diseases. | Opens the door to attempts at altering human traits not associated with disease; will increase problems of social discrimination. |
| By preventing the transmission of disease genes, the expense and risk of somatic cell therapy for multiple generations are avoided. | Involves research on early embryos and affects their offspring; creates generations of non-consenting research subjects. |
| Medicine should respond to the reproductive health needs of prospective parents at risk for transmitting serious genetic diseases. | Destroys the "natural order" (that which would occur naturally with no intervention). |

### Acceptance of Gene Therapy to Treat Genetic Mental Retardation Conditions

Gene therapy raises ethical issues related to the quality of life of people with disabilities. Some people with physical disabilities and some who are deaf say that their disabilities are not diseases and, therefore, do not need to be cured or repaired (Lane & Grodin, 1997). They believe people with disabilities can cope with their condition and lead meaningful lives, not in spite of, but with their disability. They believe that advocating for a cure indicates a belief that their lives do not have value because they have a disability.

This view is important for members of The Arc to consider. The Arc has always supported efforts to prevent mental retardation. Should we, as an organization, support gene therapy that could one day treat or cure mental retardation in those with genetic conditions? This question has been debated by interested members of The Arc over the past year or so during a series of workshops. Participants completed a questionnaire rating their agreement or disagreement with the following statements:

- Advocating for a cure for mental retardation does not devalue those who have the condition; and
- Based on my current knowledge, I believe The Arc should advocate for more funding for research to cure genetic conditions.

Table 2 illustrates the views of members who participated in the 1997 workshops. So far, close to 90 percent of those responding say that seeking a gene therapy cure for genetic conditions causing mental retardation does not devalue the person who has the condition and that The Arc should advocate for funding for gene therapy research. The Arc will continue discussing issues related to gene therapy at meetings throughout the country. Information on member's views will be used by the Board of Directors to guide decision-making regarding The Arc's position on aspects of gene therapy as needed.

### Eugenics

Historically, eugenics has been defined as "the movement devoted to improving the human species through the control of hereditary factors in mating" (Guralnik, 1976). Today, gene therapy is recognized as another approach that offers similar opportunities to improve the human species. One of the fears about human gene therapy is that the eugenics movement will again gain force.

In the early 1900s, the eugenics movement resulted in many states passing laws allowing involuntary sterilization of people with mental retardation in the belief that future generations of people with the condition would be eliminated. Although the U.S. Supreme Court in 1927 found such laws constitutional, in 1942 another decision of the Supreme Court overturned most of these laws, but not before thousands of people with mental retardation had been sterilized involuntarily. Many other people considered "less desirable" were also targeted by those believing in eugenic ideas.

Addressing the ethical, legal and social issues related to gene therapy before they arise is essential to The Arc because of past and continuing discriminatory treatment of people with mental retardation. The Arc opposes any form of discrimination toward people with mental retardation (The Arc, 1996).

**Table 2**
**Selected Members' Views on Gene Therapy**

**Advocating for cure does not devalue person**

| | # | % |
|---|---|---|
| Strongly agree or agree | 229 | 89 |
| Disagree or strongly disagree | 12 | 5 |
| Don't know | 16 | 6 |
| Total | 257 | 100 |

**The Arc should advocate for research funds to cure genetic conditions**

| | # | % |
|---|---|---|
| Strongly agree or agree | 200 | 87 |
| Disagree or strongly disagree | 13 | 6 |
| Don't know | 18 | 8 |
| Total | 231 | 101 |

### Genetic Enhancement to Improve Cognitive Abilities

Genetic enhancement would be the use of gene therapy to supply a characteristic that parents might want in a child that does not involve the treatment or prevention of disease (Gardner, 1995). For example, they may desire to control certain physical characteristics such as height and weight or to assure that their child's cognitive abilities are enhanced.

Although not available as yet, genetic enhancement to improve cognitive abilities is controversial. A major objection is that only the wealthy will be able to afford it, resulting in greater problems of social discrimination and disadvantage. Controversy surrounding this issue will continue, as some believe if a safe therapy for enhancement is developed, parents will want it for their children (Gardner, 1995).

A potential ethical issue The Arc might address is cognitive enhancement for children with mild mental retardation. If cognitive enhancement could

increase the IQ of a child with mild mental retardation, so that the child would function in the normal range, should it be considered? Currently, it is not considered acceptable to use gene therapy to treat conditions that are not diseases. Is mild mental retardation a disease that needs to be treated or a condition that does not justify a need for treatment? Walters and Palmer (1997) suggest that intellectual genetic enhancement that allows people with mental retardation to achieve functioning within the normal range is acceptable ethically. Even though such a treatment for mild mental retardation does not yet exist and may never exist, members of The Arc need to be involved proactively in discussing genetic enhancement before any policy governing its use is enacted.

### Allocation of Resources to Gene Therapy Research for Mental Retardation

At this time, gene therapy research is expensive. Assuming it remains so, there are concerns about how to allocate fairly the resources toward such research. Currently, much government and private research is focusing on conditions affecting many people (cancer, for example) where there is great potential for helping large numbers of individuals.

This raises questions about which conditions and diseases should be targeted in developing treatments for mental retardation and who decides. Clearly, most genetically caused mental retardation is of low incidence, affecting few numbers of people, ranging from 1 in 1,000 to 1 in 100,000 or fewer (Moser, 1995 ). Given the tendency to select disorders for gene therapy in which cost effectiveness is a strong force, there is concern about access to funding for genetic disorders causing mental retardation (Fletcher, 1995). Within mental retardation gene therapy research, there is a further question of fairness. Should limited resources be allocated to those genetic conditions that cause mental retardation in the greatest number of people or to those that cause the most severe forms of mental retardation? These are questions for discussion within The Arc.

### Participation of Children in Gene Therapy Research Studies

Infants and young children will be the subjects of most gene therapy research related to treating mental retardation, because the therapy must be applied before the child suffers irreversible brain damage. Research involving children requires heightened ethical sensitivity because of their vulnerability (Fletcher, 1995). First, there must be assurance that children will benefit from participation in the research. Their participation must be voluntary and informed (by them and their legal representatives). The selection of children for the research must be fair, and the research itself must be safe (Fletcher, 1995). To ensure safety, the research procedures should be tested first on animals, followed by adults and older children, before using young children with disabilities (Batshaw, 1997). The issue of fair selection for gene therapy research relates to the issue of allocation of resources, that is, how diseases or conditions are selected and how research subjects are selected given resource limitations.

Before a gene therapy study involving human subjects begins, researchers must obtain participants' informed consent for participation in the research. Informed consent is an acknowledgment by an individual that he/she understands the risks and benefits of a procedure, the possible alternatives to having the procedure, and the means that will be used to minimize risks. Children under age 18 cannot legally give informed consent. Their parents or guardians must sign for them. However, federal regulations require that researchers seek "assent" verbally from children age 7 and older. Assent means that the child knows he/she is in a research project and has some knowledge about its risks and benefits (Wertz, 1997). If a child has mental retardation, parents will have to determine if their child can understand the nature of the research and what is involved. Children who are capable of giving an informed refusal to experimental gene therapy should not be coerced to participate (Fletcher, 1995).

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# Role of Families in Helping Shape Views on Ethical Issues

Genetic research and diseases are changing the world in which we live. It is important for families potentially affected by the knowledge gained from research to become involved by becoming educated and by expressing their personal views/opinions. Human gene therapy research has been widely scrutinized since scientists began requesting funds for its support. The ethical issues have been widely debated by scientists, ethicists and others. However, few voices from families directly affected by a genetic condition have been heard.

As a family member, you may think you can have very little impact on what scientists do. Not true! Your opinions are important. By keeping informed about the issues as they affect you and your family and by speaking out, you can help shape what happens. You can advocate for the passage of certain laws or elect leaders who believe as you do. This is what The Arc has done historically in areas such as education, employment, social security and Medicaid with significant success. It is also important for you to make informed personal choices regarding participation in gene therapy research for you and your family.

As families affected by mental retardation, all of us must continue to advocate for understanding and acceptance of the condition and fair treatment of citizens with mental retardation. We must ensure that genetic technology offering a treatment for these conditions does not create a less accepting attitude within society toward people who have mental retardation. We must continue advocating for their opportunity and right to live full and satisfying lives in communities across the nation, regardless of the possibility of cure.

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